Chapter 7:
EYE CORROSION/IRRITATION

DEFINITIONS

1. Eye corrosion is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application.

2. Eye irritation is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application.

CLASSIFICATION CRITERIA FOR SUBSTANCES

Considerations

3. A tiered testing and evaluation scheme is presented that combines pre-existing information on local corrosivity and on eye irritation (including data relating to historical human or animal experience) as well as considerations on structure-activity relationships (SAR) or structure-property relationships (SPR) and the output of validated *in vitro* tests in order to avoid unnecessary animal testing.

4. The proposals for classification of eye irritation and serious damage to the eye include elements that are harmonised and will be used by all authorities as well as optional subcategories that will be applied by only some authorities (e.g., authorities classifying pesticides).

5. The harmonised system includes guidance for the use of initial considerations, that is those data elements that are evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard classes for local lesions on the eyes.

6. Before there is any *in vivo* dermal or eye irritation/corrosion testing all existing information on a test material should be reviewed. Preliminary decisions can often be made from them as to whether an agent is corrosive. If a test material can be classified, no testing is required. A highly recommended way of evaluating existing information on agents or of approaching new uninvestigated substances, is to utilise a tier testing strategy for eye irritation/corrosion.

7. Several factors should be considered in determining the eye damage or irritation potential of chemicals before testing is undertaken. Accumulated human and animal experience should be the first line of analysis, as it gives information directly referable to effects on the eye. In some cases enough information may be available from structurally related compounds to make hazard decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5, may indicate corrosive effects, especially when buffering capacity is known. Such agents are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of eye irritation/corrosion in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted may be used to make classification decisions.

8. All the above information that is available on a chemical should be used in determining the need for *in vivo* eye irritation testing. Although information might be gained from the evaluation of single

parameters within a tier (e.g., caustic alkalies with extreme pH should be considered as local corrosives), there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis should be placed upon expert judgement considering human experience with the substance, followed by the outcome of skin irritation testing and of well validated alternative methods. Animal testing with corrosive substances should be avoided whenever possible.

9. A tiered approach to the evaluation of initial information should be considered, where applicable recognising that all elements may not be relevant in certain cases. The tiered approach explained in Figure 2 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden.

10. Where data needed for such a testing strategy cannot be required, the proposed tier testing approach demonstrates a good guidance how to organise existing information on a test material and to make a weight-of-evidence decision about hazard assessment and hazard classification - ideally without conducting new animal tests.

Figure 1: Testing and evaluation strategy for eye irritation/corrosion (see also: "Testing and evaluation strategy for skin irritation/corrosion").

Step	Parameter	Findings	Conclusions
1a	Data relating to historical human or animal experience	Severe damage to eyes Eye irritant	Category 1 Category 2
	↓ No or don't know		
1b	Data relating to historical human or animal experience →	Skin corrosive →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No or don't know		
1c	Data relating to historical human or animal experience →	Skin irritant →	No evaluation of effects on eyes; deemed to be Category 2
	↓ No or don't know		
2a	SAR/SPR →	Severe damage to eyes →	Category 1
	↓ No or don't know		

Figure 1 (cont.): Testing and evaluation strategy for eye irritation/corrosion (see also: "Testing and evaluation strategy for skin irritation/corrosion")

Step	Parameter	Findings	Conclusions
2b	SAR/SPR →	Eye irritant →	No evaluation of effects on eyes; deemed to be Category 2
	↓		
	No or don't know		
	↓		
2c	SAR/SPR →	Skin corrosive →	No evaluation of effects on eyes; deemed to be Category 1
	↓		
	No or don't know		
	↓		
3a	pH/acid or alkaline reserve →	PH ≥ 11.5 or pH ≤ 2 (considering acid or alkaline reserve) →	Category 1
	↓		
3b	2 < pH < 11.5 (no buffering potential)		
	↓		
4	Other information indicating the material is a dermal corrosive →	Yes →	No evaluation of effects on eyes; deemed to be Category 1
	↓		
	No		
	↓		
5	Is a valid *in vitro* test available to assess severe damage to eyes →	No →	Go to step 6
	↓		
5a	*In vitro* test for severe eye irritation →	Severe damage to eyes →	Category 1
	↓		
	Not a severe eye irritant		
	↓		

Figure 1 (cont.): Testing and evaluation strategy for eye irritation/corrosion (see also: "Testing and evaluation strategy for skin irritation/corrosion")

Step	Parameter	Findings	Conclusions
6	Is a valid *in vitro* test for eye irritation available		
	No →	But *in vitro* test for severe eye irritancy was negative →	Go to step 8
		In the absence of any *in vitro* test →	Go to Step 7
	↓		
	Yes ↓		
6a	*In vitro* eye irritation test →	Eye irritant →	Category 2
	↓		
	No indication of eye irritant properties		
	↓		
7	Experimentally assess skin corrosion potential (see Testing Strategy for Skin Irritation/Corrosion) →	Skin corrosive →	No evaluation of effects on eyes
	↓		
	Not corrosive →	Serious damage to eyes →	Category 1
	↓		
8	1 rabbit eye test		
	↓		
	No serious damage →	Eye irritant →	Category 2
	↓		
9	1 or 2 further rabbits Not an eye irritant		

Notes to Figure 1:

<u>Step 1a/b</u>: Data relating to historical human or animal experience: Pre-existing information on eye irritation and skin corrosion are shown separately because evaluation of skin corrosion has to be considered if there is no information on local effects on eyes. Analysis of pre-existing experience with the chemical may identify both corrosion and irritation potential for both dermal and ocular effects: i) Step 1a - reliable determination of eye irritancy basing on human

or animal experience - depends on expert judgement: In most cases human experience is based on accidental events and thus, the local effects detected after an accident have to be compared with classification criteria created for evaluation of animal test data. ii) Step 1b - evaluation of data on skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as corrosive to the eyes as well. ***(Category. 1)***

Step 2a/b: SAR (Structure Activity Relationships) / SPR (Structure Property Relationships) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR/SPR approaches. The SAR/SPR analysis may identify both corrosion and irritation potential for both dermal and ocular effects: i) Step 2a - reliable determination of eye irritancy only by theoretical evaluations - in most cases it will only be appropriate for substances that are homologous to agents with very well known properties. ii) Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as corrosive to the eyes as well. ***(Category 1)***

Step 3: pH extremes like <2 and >11.5 may indicate strong local effects, especially in combination with assessment of acid or alkaline reserve (see annexed draft of a respective guideline), substances exhibiting such physico-chemical properties should be considered as corrosive to eyes. ***(Category. 1)***

Step 4: All attainable information should be used, including probable human experience. But this information should be restricted to that which pre-exists (e.g. the results of a dermal LD50 test or historical information on dermal corrosion).

Step 5: These must be alternative methods for the assessment of severe eye irritation/corrosion or serious damage to eyes (e.g., irreversible corneal opacity) which have been validated in accordance with internationally agreed principles and criteria (see "General Considerations" of Chapter 3).

Step 6: At present this step seems not be achievable in the near future. Validated alternative methods for the reliable assessment of (reversible) eye irritation need to be worked out.

Step 7: In the absence of any other relevant information, it is essential to obtain this via an internationally recognised corrosion/irritation test before proceeding to a rabbit eye irritation test. This must be conducted in a staged manner. If possible, this should be achieved using a validated, accepted in vitro skin corrosivity assay. If this is not available, then the assessment should be completed using animal tests (see the skin irritation/corrosion strategy).

Step 8: Staged assessment of eye irritation in vivo. If in a limit test with one rabbit serious damage to eyes/severe eye irritation/corrosion is detected no further testing is needed.

Step 9: Only two animals may be employed for irritation testing (including the one used for evaluation of possible severe effects) if these two animals give concordant clearly irritant or clearly non-irritant responses. In the case of different or borderline responses a third animal is needed. Depending on the result of this three-animal test, classification may be required or not.

Irreversible effects on the eye / serious damage to eyes

11. A single harmonised hazard category is adopted for substances that have the potential to damage the eyes seriously. This hazard category - Category 1(irreversible effects on the eye) - includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification: Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21 days observation period.

Table 1: Irreversible Eye Effects Categories.

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:

- at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days

  and/or

- at least in 2 of 3 tested animals a positive response of:

  corneal opacity ≥ 3 and/or
  iritis > 1.5

  calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

12. The use of human data is discussed under "General Considerations" in Chapter 3.

Reversible effects on the eye

13. A single category is adopted for substances that have the potential to induce reversible eye irritation. This single hazard category provides the option to identify within the category a sub-category for substances inducing eye irritant effects reversing within an observation time of 7 days.

14. Those authorities desiring one single category for classification of "eye irritation" may use the overall harmonised Category 2 (irritating to eyes): others may want to distinguish between Category 2 (irritating to the eyes) and Category 2A (mildly irritating to eyes).

Table 2: Reversible Eye Effects Categories.

An eye irritant Category 2A (irritating to eyes) is a test material that produces:

- at least in 2 of 3 tested animals a positive response of:

  corneal opacity ≥ 1 and/or
  iritis ≥ 1, and/or
  conjunctival redness≥ 2

  conjunctival oedema (chemosis) ≥ 2

  calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and

- which fully reverses within an observation period of normally 21 days

Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

15. For those chemicals where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of Mixtures When Data are Available for the Complete Mixture

16. The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these endpoints.

17. Unlike other endpoints, there are alternative tests available for skin corrosivity of certain classes of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for eye and skin corrosion and irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered corrosive (Eye Category 1) if it has a pH of 2 or less or 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or preparation may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

Classification of Mixtures when Data are not Available for the Complete Mixture

Bridging Principles

18. Where the mixture itself has not been tested to determine its skin and eye irritation/corrosion, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, this data will be used in accordance with the following agreed bridging rules.

This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

Dilution

19. If a mixture is diluted with a diluent which has an equivalent or lower corrosivity/irritancy classification than the least corrosive/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in paragraphs 25-30 could be applied.

Batching

20. The irritation/corrosion potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, new classification is necessary.

Concentration of Mixtures of the Highest Corrosion / Irritation Class

21. If a tested mixture classified in the highest subcategory for corrosion is concentrated, a more concentrated mixture should be classified in the highest corrosion subcategories without additional testing. If a tested mixture classified in the highest category for skin/eye irritation is concentrated and does not contain corrosive ingredients, a more concentrated mixture should be classified in the highest irritation category without additional testing.

22. If mixtures A and B are in the same irritation/corrosion toxicity category and mixture C is made in which the toxicologically active ingredients have concentrations intermediate to those in mixtures A and B, then mixture C is assumed to be in the same irritation/corrosion category as A and B. Note that the identity of the ingredients is the same in all three mixtures.

Substantially Similar Mixtures

23. Given the following:

a). Two mixtures (i.) A +B
(ii.) C + B

b). The concentration of ingredient B is essentially the same in both mixtures.

c). The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii)

d). Data on irritation/corrosion for A and C are available and substantially equivalent, i.e., they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified by testing, mixture (ii) can be assigned in the same category.

Aerosols

24. An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolised form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[1].

1. Bridging rules apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognised.

Classification of Mixtures when Data are Available for All Components or Only for Some Components of the Mixture.

25. In order to make use of all available data for purposes of classifying the eye irritation/corrosion hazards of the mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

> The "relevant ingredients" of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g., in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for eye irritation/corrosion.

26. In general, the approach to classification of mixtures as irritant or corrosive to the eye when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such components exceeds a threshold concentration limit.

27. Table 3 below provides the concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive for the eye.

28. Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 24 and 25 might not work given that many of such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria (see paragraph 15) since pH will be a better indicator of corrosion than the concentration limits of Table 3. Mixtures containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3 due to chemical characteristics that make this approach unworkable, the mixture will be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3 does not apply is summarised in Table 4 below.

29. On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration cut-off levels mentioned in Tables 3-4. In these cases the mixture could be classified according to that data (see also Chapter 3 – Use of Cut-Off Values). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration cut-off levels mentioned in Tables 3-4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy should be applied as referred to in paragraph 7 and explained in detail in the chapter on classification of substances for eye hazards

30. If there is data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also Chapter 3 – Use of Cut-Off Values).

Table 3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixtures as hazardous to the eye (Category 1 or 2).

Sum of Ingredients Classified as:	Concentration triggering classification of a mixture as:	
	Eye	
	Irreversible	Reversible
	Category 1	Category 2
Eye or Skin Category 1	≥ 3%	≥1% but < 3%
Eye Category 2/2A		≥10%
(10 x Eye Category 1) + Eye Category 2/2A		≥10%
Skin Category 1 + Eye Category 1	≥ 3%	≥1% but <3%
10 x (Skin Category 1 + Eye Category 1) + Eye Category 2/2A		≥10%

Table 4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye.

Ingredient:	Concentration:	Mixture classified as:
		Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

HAZARD COMMUNICATION

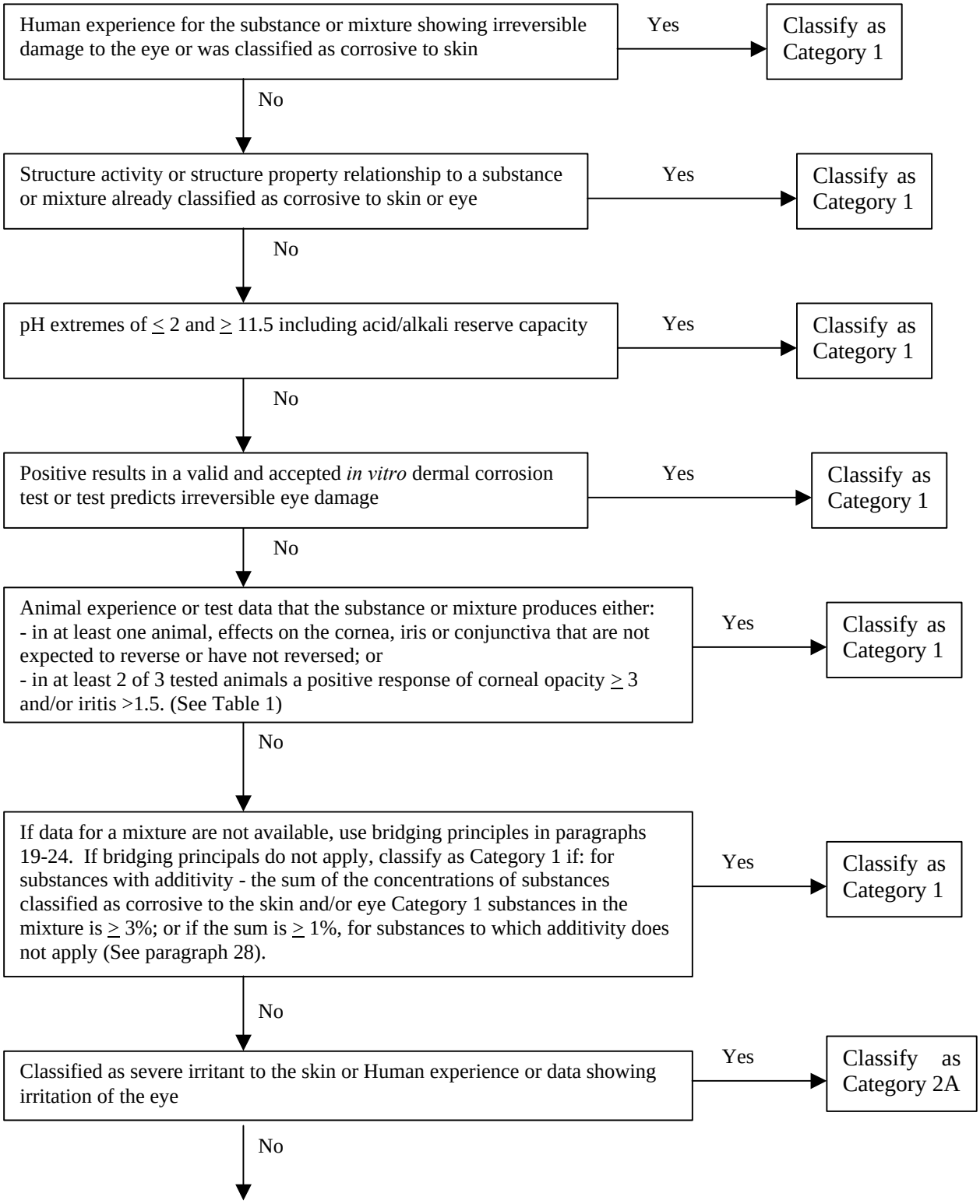
Allocation of Label Elements

31. General and specific considerations concerning labelling requirements are provided in Chapter 4. Annex 5 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

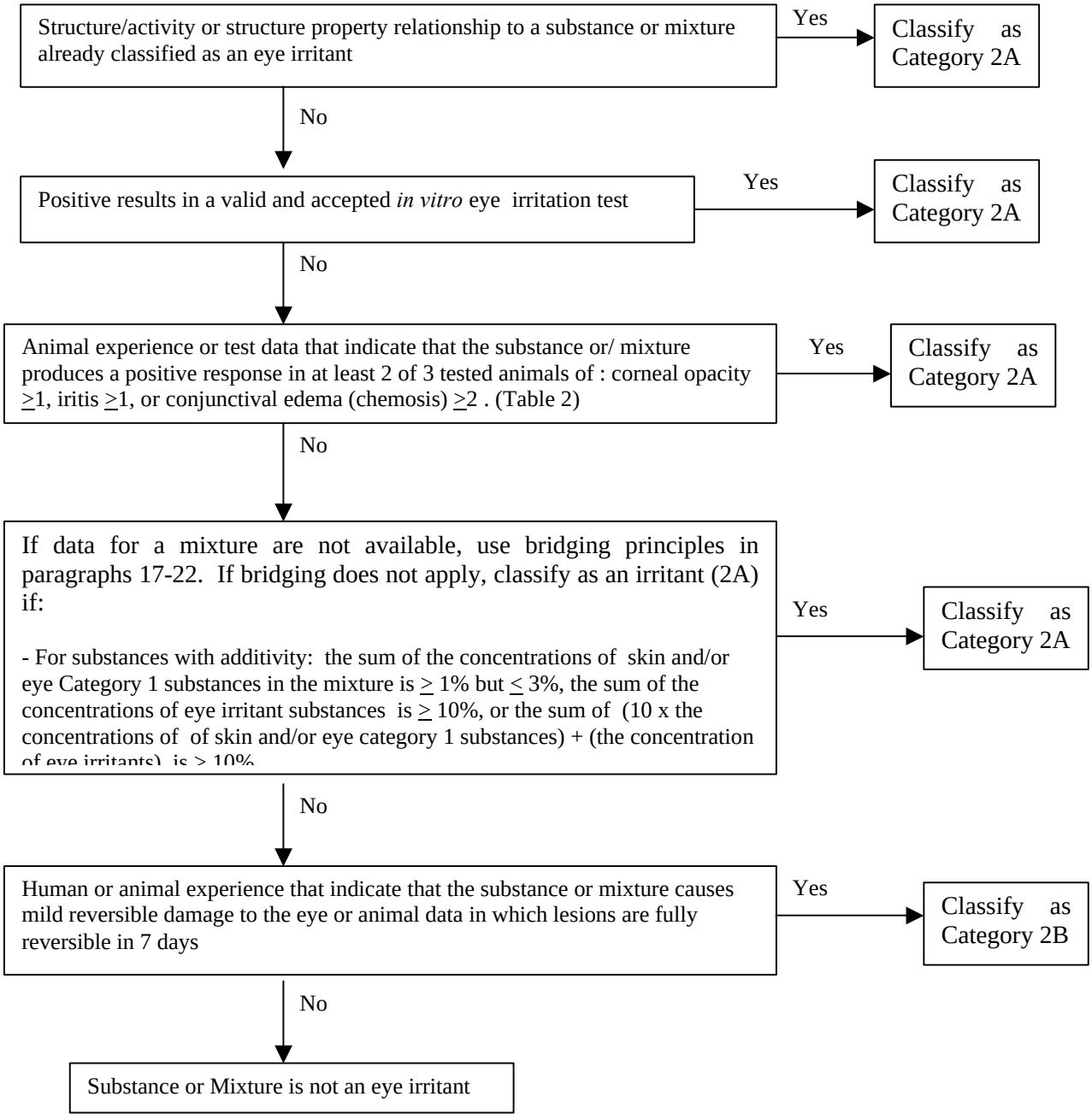
Table 5: Label Elements for Eye corrosion/irritation

	Category 1	**Category 2A**	**Category 2B**
Symbol	Corrosive symbol	Exclamation mark	No symbol is used
Signal Word	Danger	Warning	Warning
Hazard Statement	Causes severe eye damage	Causes severe eye irritation	Causes eye irritation

Decision Logic for Eye Corrosion/irritation:



Continuation - Decision Logic for Eye Corrosion/irritation:



Classification and Labelling Summary for Eye Corrosion/irritation

If the substance or mixture meets one of the following criteria, classify and use corresponding communication elements. If the criteria are not met then the substance or mixture need not be classified.

Class	**Criteria** (See Figure 1 for detailed decision tree)	**Hazard Communication Elements**	
Category 1 Irreversible Effects	• Classification as corrosive to skin; • Human experience or data showing damage to the eye which is not fully reversible within 21 days; • Structure/activity or structure property relationship to a substance or mixture already classified as corrosive; • pH extremes of $\leq$ 2 and $\geq$ 11.5 including buffering capacity; • Positive results in a valid and accepted *in vitro* test to assess severe damage to eyes; or • Animal experience or test data that the substance or mixture produces either (1) in at least one animal, effects on the cornea, iris or conjunctiva that are not expected to reverse or have not reversed; or (2) in at least 2 of 3 tested animals a positive response of corneal opacity $\geq$ 3 and/or iritis >1.5. (See Table 1) .If data for a mixture are not available, use bridging principles in paragraphs 19-24. If bridging principals do not apply, classify as Category 1 if the sum of the concentrations of substances classified as corrosive to the skin and/or eye Category 1 substances in the mixture is $\geq$ 3% (for substances with additivity), or $\geq$ 1% (for substances to which additivity does not apply). See paragraph 28.	*Signal Word*	Danger
		Symbol	Corrosive symbol
		Hazard Statement	Causes severe eye damage
Category 2A Irritant	• Classification as severe skin irritant; • Human experience or data showing production of changes in the eye which are fully reversible within 21 days; • Structure/activity or structure property relationship to a substance or mixture already classified as an eye irritant; • Positive results in a valid and accepted *in vitro* eye irritation test; or • Animal experience or test data that indicate that the substance/mixture produces a positive response in at least 2 of 3 tested animals of : corneal opacity $\geq$1, iritis $\geq$1, or conjunctival edema (chemosis) $\geq$2 . (Table 2) If data for a mixture are not available, use bridging principles in paragraphs 17-22. If bridging does not apply, classify as an irritant (2A) if: • For substances with additivity: the sum of the concentrations of skin and/or eye Category 1 substances in the mixture is $\geq$ 1% but $\leq$ 3%; the sum of the concentrations of eye irritant substances is $\geq$ 10%; or the sum of (10 x the concentrations of of skin and/or eye category 1 substances) + (the concentrations of eye irritants) is $\geq$ 10% • For substances to which additivity does not apply): the sum of the concentrations of eye irritant ingredients is $\geq$ 3% (See paragraph 28)	*Signal Word*	Warning
		Symbol	Exclamation mark
		Hazard Statement	Causes severe eye irritation
Category 2B Mild Irritant	• Human experience or data showing production of mild eye irritation; • Animal experience or test data that indicate that the lesions are fully reversible within 7 days. (See Table 2)	*Signal Word*	Warning
		Symbol	No symbol
		Hazard Statement	Causes eye irritation

EXAMPLES

To be provide later this week.